AMENDMENT

Please amend the application without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents as follows.

In the Claims

1. (Original) A method for modulating an immune response comprising administering a modulator of Notch intracellular domain (Notch IC) protease activity.

2. (Original) The method of claim 1, wherein the modulator of Notch IC is an agonist of presenilin or presenilin-dependent gamma-secretase.

3. (Original) The method of claim 2, wherein the presenilin is Presenilin-1 (PS1) or Presenilin-2 (PS2).

4. (Original) The method of claim 2, wherein the agonist is selected from the group consisting of polypeptides, fragments thereof, linear peptides, cyclic peptides, nucleic acids encoding therefor, synthetic compounds, natural compounds, low molecular weight organic compounds, low molecular weight inorganic compounds and antibodies.

5. (Original) The method of claim 1, further comprising administering a modulator of Notch signalling pathway.

6. (Original) The method of claim 5, wherein the modulator of Notch IC is an agonist of presenilin or presenilin-dependent gamma-secretase.

7. (Original) The method of claim 6, wherein the presenilin is Presenilin-1 (PS1) or Presenilin-2 (PS2).

8. (Original) The method of claim 6, wherein the agonist is selected from the group consisting of polypeptides, fragments thereof, linear peptides, cyclic peptides, nucleic acids encoding therefor, synthetic compounds, natural compounds, low molecular weight organic compounds, low molecular weight inorganic compounds and antibodies.

9. (Original) The method of claim 6, wherein the modulator of the Notch signalling pathway is an agent that up-regulates the Notch signalling pathway.

10. (Original) The method of claim 7, wherein the agonist of presenilin is Nicastrin or ALG-3, or a nucleic acid sequence encoding therefor.

11. (Original) The method of claim 6, wherein the modulator of the Notch signalling pathway is an agent that down-regulates the Notch signalling pathway.

12. (Original) The method of claim 11, wherein the agonist of presenilin is 26S proteasome or Sel 10 or a nucleic acid sequence encoding therefor.

13. (Original) The method of claim 7, wherein the agent that up-regulates the Notch signalling pathway is a polypeptide selected from the group consisting of Notch ligands, Noggin, Chordin, Follistatin, Xnr3, FGF, derivatives, fragments, variants and homologues thereof, and immunosuppressive cytokines, or is a combination thereof, or is a nucleic acid sequence encoding therefor.

14. (Original) The method of claim 11, wherein the agent that down-regulates the Notch signalling pathway is a polypeptide selected from the group consisting of a Toll-like receptor, a cytokine, a bone morphogenetic protein (BMP), a BMP receptor and an activin, or is a nucleic acid sequence encoding therefor.

15. (Original) The method of claim 1, wherein the immune response is to a selected antigen or antigenic determinant.

16. (Original) The method of claim 15, wherein the selected antigen or antigenic determinant, or a nucleic acid encoding the antigen or antigenic determinant, is administered simultaneously, contemporaneously, separately or sequentially with the modulator.

17. (Original) The method of claim 15, wherein the antigen or antigenic determinant is a tumour antigen or antigenic determinant or an antigen or antigenic determinant of a pathogen.

18. (Original) The method of claim 1, wherein modulating the immune response comprises modulating lymphocyte activity.

19. (Original) The method of claim 1, wherein modulating the immune response comprises modulating T-cell activity.

20. (Original) The method of claim 19, wherein the T-cell is an effector T-cell.

21. (Original) The method of claim 19, wherein the T-cell is a helper (Th) T-cell.

22. (Original) The method of claim 21, wherein the modulator is an inhibitor of Notch IC protease activity, and wherein helper (Th) T-cell activity is increased.

23. (Original) The method of claim 21, wherein the modulator is an enhancer of Notch IC protease activity, and wherein helper (Th) T-cell activity is decreased.

24. (Original) The method of claim 19, wherein the T-cell is a cytotoxic (Tc) T-cell.

25. (Original) The method of claim 24, wherein the modulator is an inhibitor of Notch IC protease activity, and wherein cytotoxic (Tc) T-cell activity is increased.

26. (Original) The method of claim 24, wherein the modulator is an enhancer of Notch IC protease activity, and wherein cytotoxic (Tc) T-cell activity is decreased.

27. (Original) The method of claim 19, wherein the T-cell is a regulatory (T reg) T-cell.

28. (Original) The method of claim 27, wherein the modulator is an inhibitor of Notch IC protease activity, and wherein regulatory (T reg) T-cell activity is decreased.

29. (Original) The method of claim 27, wherein the modulator is an enhancer of Notch IC protease activity, and wherein regulatory (T reg) T-cell activity is increased.

30. (Original) The method of claim 19, wherein the T-cell is a Tr1 regulatory T-cell.

31. (Original) The method of claim 30, wherein the modulator is an inhibitor of Notch IC protease activity, and wherein Tr1 regulatory T-cell activity is decreased.

32. (Original) The method of claim 30, wherein the modulator is an enhancer of Notch IC protease activity, and wherein Tr1 regulatory T-cell activity is increased.

33. (Original) The method of claim 19, wherein T-cell is a Th3 regulatory T-cell.

34. (Original) The method of claim 33, wherein the modulator is an inhibitor of Notch IC protease activity, and wherein Th3 regulatory T-cell activity is decreased.

35. (Original) The method of claim 33, wherein the modulator is an enhancer of Notch IC protease activity, and wherein Th3 regulatory T-cell activity is increased.

36. (Original) The method of claim 1, wherein the modulator is administered to a subject *in vivo*.

37. (Original) The method of claim 1, wherein the modulator is administered to a cell *ex vivo*.

38. (Original) The method of claim 1, wherein modulating the immune response treats a T cell mediated disease or infection.

39. (Original) The method of claim 38, wherein the T cell mediated disease or infection is one or more of allergy, autoimmunity, graft rejection, tumour induced aberrations to the T cell, and infectious diseases.

40. (Original) The method of claim 1, wherein the modulator is an enhancer of Notch IC protease activity, when wherein modulating the immune response treats inflammation or an inflammatory condition.

41. (Original) The method of claim 1, wherein a subject's immune system is stimulated.

42. (Original) A method for modulating cytokine expression comprising administering a modulator of Notch intracellular domain (Notch IC) protease activity.

43. (Original) The method of claim 42, wherein the cytokine is a lymphokine.

44. (Original) The method of claim 42, wherein the cytokine is a monokine.

45. (Original) The method of claim 42, wherein the cytokine expression is Notch-mediated cytokine expression.

46. (Original) The method of claim 42, wherein the cytokine is selected from the group consisting of IL-10, IL-5, IL-4, IL-2, TNF-alpha, IFN-gamma and IL-13.

47. (Original) The method of claim 46, wherein the cytokine is IL-10 or IL-4, wherein the modulator is an inhibitor of Notch IC protease activity, and wherein expression of the cytokine is decreased.

48. (Original) The method of claim 46, wherein the cytokine is IL-10 or IL-4, wherein the modulator is an enhancer of Notch IC protease activity, and wherein expression of the cytokine is increased.

49. (Original) The method of claim 46, wherein the cytokine is IL-10.

50. (Original) The method of claim 46, wherein the cytokine is IL-4.

51. (Original) The method of claim 46, wherein the cytokine is IL-2, IL-5, TNF-alpha, IFN-gamma or IL-13, wherein the modulator is an inhibitor of Notch IC protease activity, and wherein expression of the cytokine is increased.

52. (Original) The method of claim 46, wherein the cytokine is IL-2, IL-5, TNF-alpha, IFN-gamma or IL-13, wherein the modulator is an enhancer of Notch IC protease activity, and wherein expression of the cytokine is decreased.

53. (Original) The method of claim 46, wherein the cytokine is IL-2.

54. (Original) The method of claim 46, wherein the cytokine is IL-5.

55. (Original) The method of claim 46, wherein the cytokine is TNF-alpha.

56. (Original) The method of claim 46, wherein the cytokine is IFN-gamma.

57. (Original) The method of claim 46, wherein the cytokine is IL-13.

58. (Original) The method of claim 46, wherein the modulator is an enhancer of Notch IC protease activity, and wherein IL-10 expression is increased and IL-5 expression is decreased.

59. (Original) The method of claim 46, wherein the modulator is an enhancer of Notch IC protease activity, and wherein IL-10 expression is increased and IL-2, IFN-gamma, IL-5, IL-13 and TNF-alpha expression are decreased.

60. (Original) The method of claim 46, wherein the modulator is an inhibitor of Notch IC protease activity, and wherein IL-10 expression is decreased and IL-5 expression is increased.

61. (Original) The method of claim 46, wherein the modulator is an inhibitor of Notch IC protease activity, and wherein IL-10 expression is decreased and IL-2, IFN-gamma, IL-5, IL-13 and TNF-alpha expression are increased.

62. (Original) The method of claim 42, wherein cytokine expression is modified in leukocytes, fibroblasts or epithelial cells.

63. (Original) The method of claim 42, wherein cytokine expression is modified in cells selected from the group consisting of dendritic cells, lymphocytes, macrophages, progenitors therof, and tissue-specific derivatives thereof.

64. (Original) The method of claim 63, wherein the cells are lymphocytes or macrophages.

65. (Original) The method of claim 42, wherein the modulator is administered to a subject *in vivo*.

66. (Original) The method of claim 42, wherein the modulator is administered to a cell *ex vivo*.

67. (Original) The method of claim 42, wherein modulating the immune response treats a T cell mediated disease or infection.

68. (Original) The method of claim 67, wherein the T cell mediated disease or infection is one or more of allergy, autoimmunity, graft rejection, tumour induced aberrations to the T cell, and infectious diseases.

69. (Original) The method of claim 42, wherein the modulator is an enhancer of Notch IC protease activity, when wherein modulating the immune response treats inflammation or an inflammatory condition.

70. (Original) A modulator of Notch IC protease activity for use in affecting (i) T cell mediated disease or infection, (ii) linked suppression or (iii) infectious tolerance.

71. (Original) A composition comprising the modulator of claim 70 and a modulator of the Notch signalling pathway.

72. (Original) A method for producing a lymphocyte or antigen presenting cell (APC) having tolerance to an allergen or antigen, which method comprises incubating a lymphocyte or APC obtained from a human or animal subject with (i) an agonist of presenilin or presenilin-dependent gamma-secretase and, optionally, an agent that up-regulates endogenous Notch or Notch ligand in the lymphocyte or APC and (ii) the allergen or antigen, thereby producing a lymphocyte or APC having tolerance to the allergen or antigen.

73. (Original) The method of claim 72, wherein an APC capable of inducing T cell tolerance is produced.

74. (Original) A method for producing a lymphocyte or APC having tolerance to an allergen or antigen, which method comprises incubating a lymphocyte or APC obtained from a human or animal subject with the lymphocyte or APC produced by the method of claim 72.

75. (Original) A method of suppressing an immune response to an allergen or antigen in a mammal, which method comprises administering to the mammal a lymphocyte or APC produced by the method of claim 72.

76. (Original) A method of treating a subject having a disease characterised by inappropriate lymphocyte activity, which method comprises administering to the subject a lymphocyte produced by the method of claim 72.

77. (Original) A method of treating a subject having a disease characterised by inappropriate lymphocyte activity, which method comprises administering to the subject a lymphocyte produced by the method of claim 74.

78. (Original) A method for producing, *ex vivo,* a T cell having tolerance to an allergen or antigen, which method comprises incubating a T cell obtained from a human or animal subject with an antigen presenting cell (APC), in the presence of (i) an agonist of presenilin or presenilin-dependent

gamma-secretase and, optionally, an agent that up-regulates expression of an endogenous Notch or Notch ligand in the APC or T cell and (ii) the allergen or antigen, thereby producing a T cell having tolerance to the allergen or antigen.

79. (Original) A method for producing a lymphocyte or APC having tolerance to an allergen or antigen, which method comprises incubating a lymphocyte or APC obtained from a human or animal subject with the T cell produced by the method of claim 77.

80. (Original) A method of treating a subject having a disease characterised by inappropriate lymphocyte activity, which method comprises administering to the subject a lymphocyte produced by the method of claim 79.

81. (Original) A method for enhancing the reactivity of a T cell toward a tumour cell which method comprises:

a) isolating a T cell, antigen presenting cell (APC) or tumour cell from a subject having a tumour cell present in their body;

b) exposing the T cell, APC or tumour cell to a modulator of Notch IC protease activity, optionally in the presence of an agent which reduces or prevents expression of or interaction between an endogenous Notch or Notch ligand in a T cell; and

c) re-introducing the T cell, APC or tumour cell into the subject.

82. (Original) The method of claim 81, wherein the T cell is a tumour infiltrating lymphocyte.

83. (Original) A method of vaccinating a subject against a tumour, which method comprises:

a) administering a tumour antigen expressed by cells of the tumour to the subject; and

b) exposing an APC present in the subject to a modulator of presenilin or presenilin-dependent gamma-secretase agent, optionally in the presence of an agent which reduces or prevents expression of, interaction between or processing of Notch and/or a Notch ligand in a T cell.

84. (Original) An assay for identifying modulators of Notch IC protease activity, wherein the assay comprises contacting a presenilin or presenilin-dependent gamma-secretase, in the presence of Notch and a modulator of the Notch signalling pathway, with a candidate compound and determining whether the candidate compound affects the Notch signalling pathway, thereby identifying a modulator of Notch IC protease activity, if Notch signalling is

different when the candidate compound is present than when it is absent.

85. (Original) The assay of claim 84, wherein the assay is conducted using an immune cell.

86. (Original) An assay for identifying a substance that affects the interaction of a presenilin interacting protein or presenilin-dependent gamma-secretase interacting protein with a presenilin protein or presenilin-dependent gamma-secretase, respectively, comprising:

a) providing a preparation containing: a presenilin protein or presenilin-dependent gamma-secretase; a presenilin-interacting protein or presenilin-dependent gamma-secretase, respectively; and a candidate substance; and

b) detecting whether the candidate substance affects the interaction of presenilin-interacting protein or presenilin-dependent gamma-secretase-interacting protein with presenilin protein or presenilin-dependent gamma-secretase;

thereby identifying a candidate substance that affects the interaction of a presenilin interacting protein or presenilin-dependent gamma-secretase interacting protein with a presenilin protein or presenilin-dependent gamma-secretase, respectively, if the interaction is different when the candidate substance is present in the preparation than when it is absent in the preparation.

87. (Original) The assay of claim 86, wherein the assay is conducted using an immune cell.

88. (Original) The assay of claim 86, wherein the presenilin-interacting protein is Notch or a member of the Notch signalling pathway.

89. (Original) A composition for immunomodulation comprising: (i) a modulator of Notch IC protease activity, and (ii) an antigen or antigenic determinant or a polynucleotide encoding an antigen or antigenic determinant, wherein (i) and (ii) are administered simultaneously, contemporaneously, separately or sequentially.

90. (Original) The composition of claim 89, further comprising a pharmaceutically acceptable carrier.

91. (Original) The composition of claim 89, wherein immunomodulation comprises increasing effector T cell activity.

92. (Original) The composition of claim 89, wherein the antigen or antigenic determinant is a tumour antigen or antigenic determinant or an antigen or antigenic determinant of

a pathogen.

93. (Original) A kit comprising, in one or more containers, (i) a modulator of Notch signalling pathway and (ii) a modulator of presenilin or presenilin-dependent gamma-secretase activity.

94. (Original) An adjuvant composition comprising a modulator of Notch IC protease activity.

95. (Original) A vaccine composition comprising the adjuvant composition of claim 94 and a tumour or pathogen antigen or antigenic determinant or a polynucleotide encoding a tumour or pathogen antigen or antigenic determinant.

96. (Original) The vaccine composition of claim 95 comprising a pathogen antigen or antigenic determinant in the form of a viral, fungal, parasitic or bacterial antigen or antigenic determinant, or a polynucleotide encoding a viral, fungal, parasitic or bacterial antigen or antigenic determinant.

97. (New) A method of modulating an immune response comprising administering an inhibitor of Notch IC protease activity.

98. (New) The method of claim 97, wherein the inhibitor is a gamma-secretase inhibitor.

99. (New) The method of claim 98, wherein the gamma-secretase is presenilin dependent.

100. (New) The method of claim 98, wherein the inhibitor is a small molecule inhibitor.

101. (New) The method of claim 98, wherein the inhibitor is MW167.